

# The Breast Cancer Landscape

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## Breast Cancer Incidence

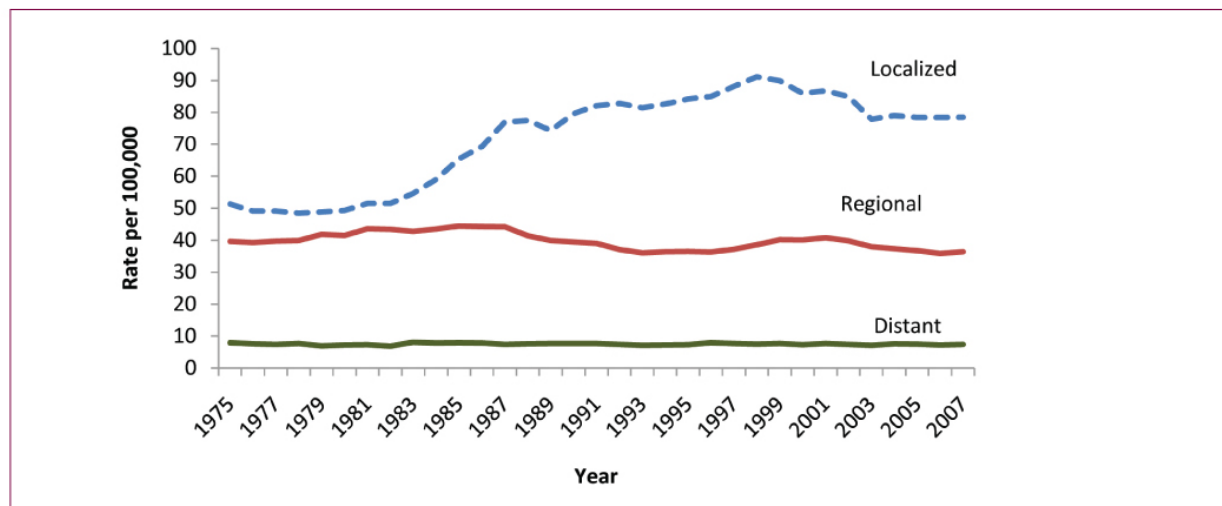
Breast cancer is a global problem. Worldwide, breast cancer accounts for nearly a quarter of all cancers in women. In 2010, there were 1.7 million women diagnosed with the disease.<sup>1</sup> In the United States, in 2014, it is estimated that more than 232,670 women and 2,360 men will be diagnosed with breast cancer.<sup>2</sup> The chance of a woman being diagnosed with breast cancer during her lifetime has increased from about 1 in 11 in 1975 to 1 in 8 today.<sup>3</sup> The number of women being diagnosed continues to increase as the number of women in age groups at risk of breast cancer increases, e.g., the “baby boomers.” However, the proportion of the population affected by the disease remains relatively constant. Recently, researchers at the National Cancer Institute (NCI) projected that the overall breast cancer incidence rate will stay the same through 2016.<sup>4</sup> The median age at diagnosis is 61.<sup>3</sup>

Because of increased screening beginning in 1980, there has been a dramatic increase in the incidence of ductal carcinoma in situ (DCIS), abnormal cells contained within the milk ducts that have not spread to other parts of the body. Most DCIS will never become invasive cancer. It is currently not possible to distinguish the DCIS that will develop into cancer from the harmless type; as a result, many women are treated with redundant interventions that are associated with potential short-term and long-term morbidities.<sup>5</sup>

## Breast Cancer Deaths

In 2010 there were 522,000 deaths globally.<sup>6</sup> In the United States, in 2014, it is estimated that 40,000 women and 430 men will die of breast cancer.<sup>2</sup> In 2035, with no major changes in prevention or treatment, it is estimated that 846,241 women will die from breast cancer worldwide.<sup>7</sup> Women do not die of breast cancer confined to the breast or draining lymph nodes. Most breast cancer deaths are due to the spread of the disease to other parts of the body, and its consequence on impairing the function of vital organs like lung, liver, and brain. As depicted in Figure 1 below, the rate of metastatic breast cancer at initial diagnosis in the United States has not changed since 1975.

## No Change in Metastatic (Distant Stage) Cancer at Initial Diagnosis



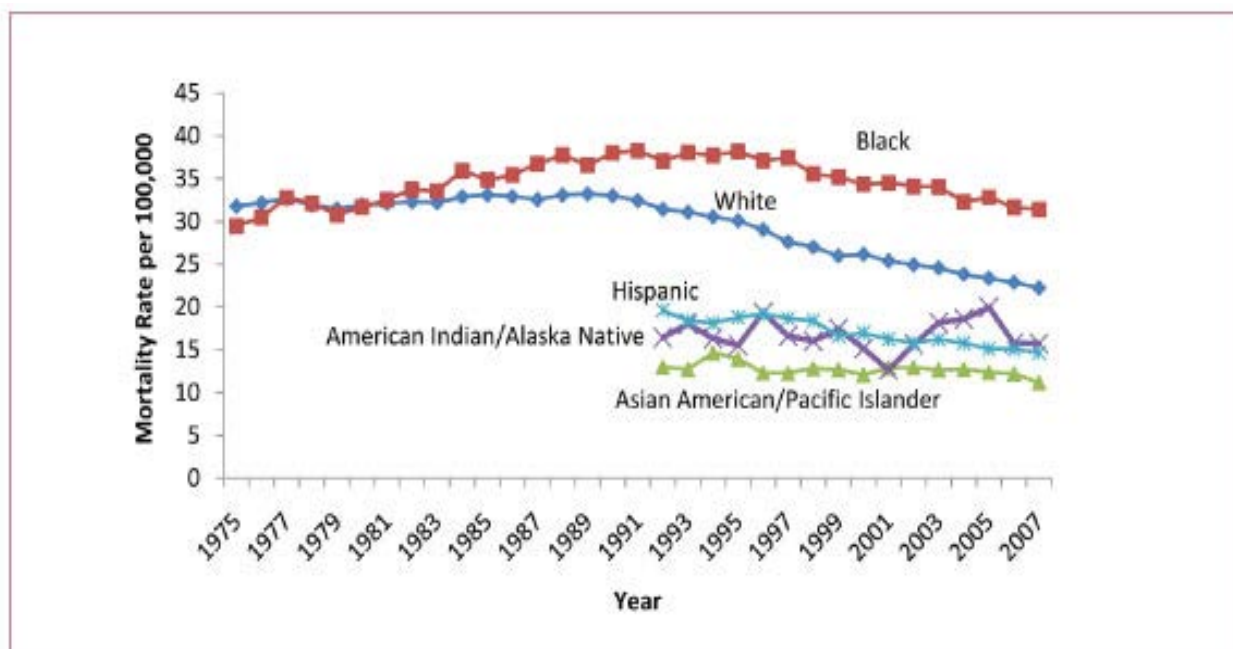
**Figure 1. Female Breast Cancer Incidence Rates\* by Stage\*\*, US, 1975-2007**

\*Rates are age-adjusted to the 2000 US standard population.

\*\*Localized – confined to primary site in breast; regional – spread to regional lymph nodes; distant – cancer has metastasized.

**Data Source:** Surveillance, Epidemiology, and End Results (SEER) Program. SEER 9 Registries, 1973-2007, National Cancer Institute, DDCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2010, based on the November 2009 submission.

Between 1975 and 1990, breast cancer mortality rates in the United States increased slightly, and then began decreasing slightly in the late 1990s for all women, with the overall highest rate of decrease in white women (Figure 2). From 2000-2007, breast cancer mortality rates decreased at an average rate of 1.9% per year.<sup>6</sup>



**Figure 2. Female Breast Cancer Mortality Rates\* by Race and Ethnicity, US, 1975-2007**

\*Rates are age-adjusted to the 2000 US standard population.

**Data Source:** US Mortality Files, National Center for Health Statics, CDC. Rates for American Indian/Alaska Native are based on the CHSDA (Contract Health Service Delivery Area; counties).

There has been no acceleration in the rate of decrease in mortality (1.9%). The cause of the slight decrease is multifactorial and has been attributed to such factors as reduced use of hormone replacement therapy, behavioral changes (e.g., reduced smoking), earlier detection, and improved treatments.<sup>7</sup>

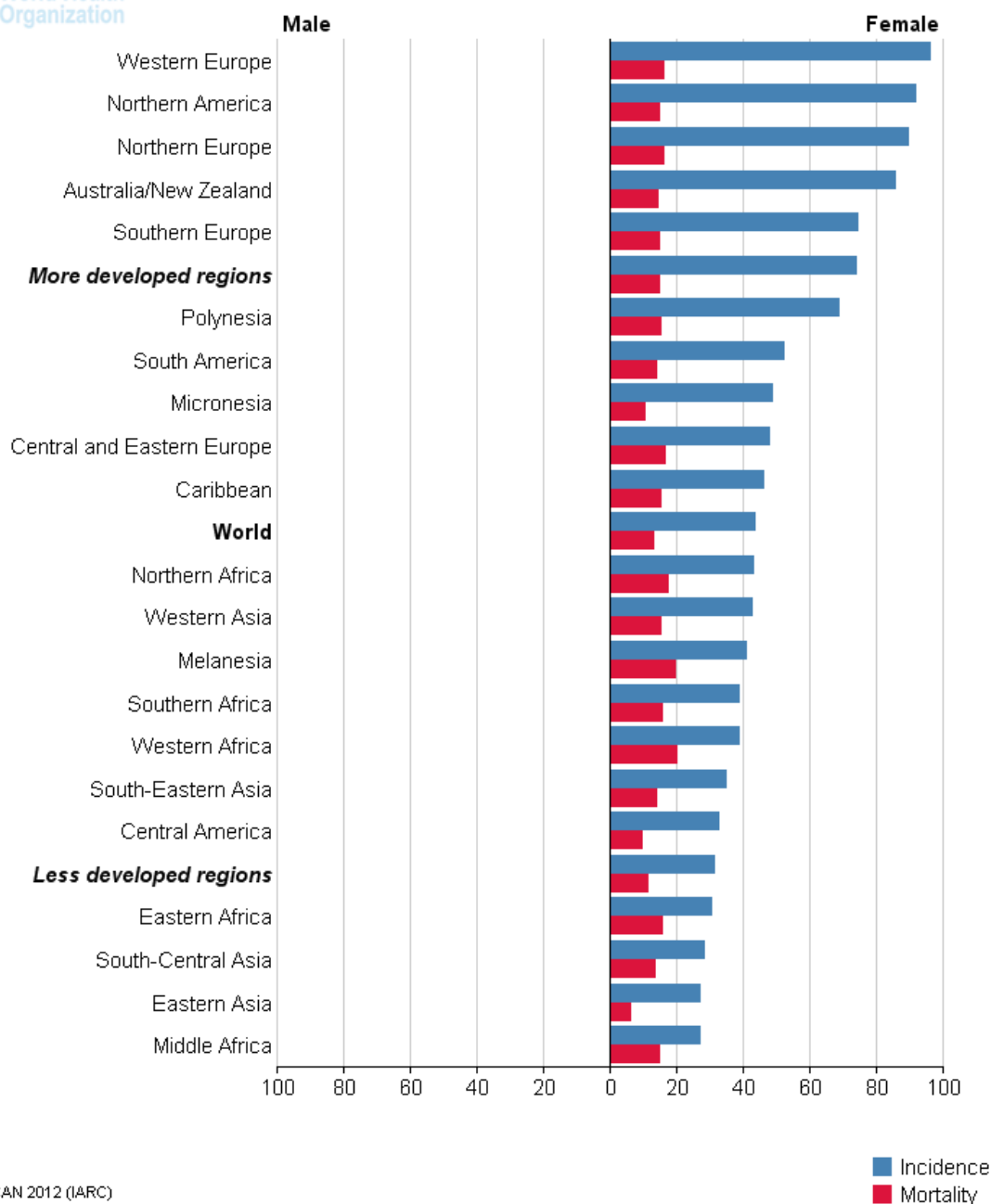
**Note:** Five-year survival rates, though often used, are not a measure of progress. The NCI reports that 5-year breast cancer survival is 98% for women who are diagnosed with localized disease. However, survival rates are skewed by screening: the more women that are screened, the more early cancers are found, resulting in a larger denominator of breast cancer cases, i.e., more women will be counted as alive at 5 years. Evidence suggests that many women would not have died of breast cancer in that time frame, even if they had not been screened. In addition, these numbers do not take recurrence into account. A sizable proportion of the women reported to have survived for 5 years will have their breast cancer recur.<sup>8</sup>

While incidence across global regions varies significantly, this is primarily a function of screening practices in more developed countries. Differences in mortality rates are much less appreciable.<sup>8</sup>

International Agency for Research on Cancer



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**Figure 3. World Incidence and Mortality Rates**

## Recurrence and Metastatic Disease

We still do not know how to prevent recurrence and metastasis for any individual woman. An estimated 20% to 30% of women diagnosed with invasive breast cancer will have a recurrence and may eventually die of their disease.<sup>9</sup>

An estimated 90% of deaths due to breast cancer are a consequence of metastatic disease, whether the cancer was metastatic at diagnosis or a metastatic recurrence that developed later.

It has been estimated that approximately 155,000 women are living with metastatic breast cancer in the United States, and this estimate was projected to rise to 162,000 by the end of 2011, according to one expert.<sup>10</sup> The exact numbers are not known; neither is information available on historical trends. While researchers have identified treatments that sometimes shrink or slow metastatic tumors, such as estrogen blockers, radiation, and chemotherapy, they are most often temporary. ***Treatments to permanently eradicate metastasis do not exist. There is no cure once metastatic disease has occurred.***

Median survival with metastatic breast cancer is 3 years, and there has been no statistically significant change in over 20 years.<sup>11</sup> Recent estimates are that, with current historical trends, median survival will increase by 6 months by the year 2021.<sup>12</sup>

While the risk of recurrence is greater in the first 5 years after a diagnosis of estrogen receptor (ER)-negative breast cancer, patients with ER-positive tumors have a consistent long-term risk of death from breast cancer and a greater risk after 7 years.<sup>13, 14</sup> Approximately 75% of breast cancer is ER-positive, and most breast cancer deaths occur in ER-positive women.

## Risk Factors

Over the years, epidemiologic studies have established a handful of risk factors for breast cancer. These studies provide information about risk factors on a population level, but have not proven to be effective in predicting an individual's risk of breast cancer. Further, it has been estimated that no more than 55% of breast cancer is explained by the risk factors identified thus far.<sup>15</sup> Evidence attributes the majority of cancers to not one single factor but various physical, environmental, and genetic factors. Factors affecting obesity, immunity, and the tumor's environment within the body, as well as exogenous environmental exposures are all examples of variables in the development of disease.<sup>16, 17</sup>

Most risk factors are not modifiable, including age, family history, reproductive history, BRCA status, and breast density. The amount of lifetime exposure of breast tissue to circulating ovarian hormones is only partially under one's control—modifiable with respect to exogenous hormone use. Similarly, the age at which menarche and menopause occur is generally out of one's control.

Other risk factors are potentially modifiable, including obesity reduction, avoidance of use of combined estrogen and progestin menopausal hormones, reduced alcohol consumption and smoking, and increased physical activity. However, all of these factors are only weakly to

moderately associated with breast cancer risk, with relative risks of <2.0. There is also mixed evidence in relation to the impact of various commonly used medications on breast cancer risk, with some emerging evidence that perhaps bisphosphonates and metformin may lower breast cancer risk.<sup>18, 19, 20, 21</sup>

Radiation exposure is a well-established risk factor for breast cancer, and secondary breast cancer is strongly associated with high-dose radiation therapy to the chest for young women between the ages of 10 and 30 years treated for cancers, such as Hodgkin's lymphoma.<sup>2</sup> Studies have demonstrated that women who had their first exposure to medical radiation procedures during childhood, even at lower doses, had a greater increase in the risk of breast cancer than those who were first exposed at older ages.<sup>22</sup> This higher risk begins about 8 years after such exposure and continues to be elevated for more than 25 years.

Importantly, evidence is emerging that BRCA mutation carriers are exquisitely sensitive to the effect of radiation exposure through diagnostic procedures, with their risk of breast cancer increasing in a dose-dependent fashion.<sup>23, 24</sup>

## Breast Cancer Treatments

For decades, breast cancer treatment has included surgery, radiation therapy, chemotherapy, and/or hormonal therapy, and within the past 15 years, targeted antibody therapy. Some of the most significant changes in treatment has been in doing less surgery; for example, moving from radical mastectomy to lumpectomy and radiation therapy, and removing fewer lymph nodes.<sup>25</sup> These two developments have had a major impact on improving quality of life. However, while important, these changes in standard of care do not change the mortality statistics.

Breast cancer can be divided into different subtypes, based on the biology of the tumor. The majority of women with breast cancer still receive the same treatment as though all breast cancers were the same.<sup>26</sup>

There are treatments targeted to some subtypes. For example, hormonal therapies, such as aromatase inhibitors and selective ER modulators, target ER-positive breast cancer. Trastuzumab, a monoclonal antibody, targets HER2-overexpressing breast cancer. Importantly, de novo and acquired resistance are major issues with all known targeted therapies.

A meta-analysis of clinical studies on early breast cancer found a reduction in risk of recurrence for all women treated with chemotherapy, but a benefit in survival only for younger women.<sup>27, 28</sup> For combination chemotherapy, studies showed an absolute improvement of only 7-11% in 10-year survival for younger women and of 2-3% for women ages 50-69, the age range when the majority of breast cancers are diagnosed.<sup>29</sup>

Standard adjuvant therapies have only a small (5% to 10%) impact on disease-specific survival. Currently, adjuvant therapies are given to all individuals with breast cancer, but benefit only a small proportion. This nonspecific approach derives from the fact that we do not know how to reliably identify which cancers will recur.

Radiation therapy (RT) is coupled with breast conserving surgery as a standard of care, based on the 1976 randomized trial that showed a 9% (although not statistically significant) decrease in breast cancer deaths with RT combined with lumpectomy.<sup>30</sup> A subsequent meta-analysis showed a 5% reduction in 15-year breast cancer mortality risk.<sup>31</sup>

The cost of treating breast cancer continues to rise. The national cost of cancer care in 2010 was estimated to be \$124.6 billion, with female breast cancer care leading all cancer sites at an estimated \$16.5 billion.<sup>32</sup>

## **Morbidity and Mortality Caused by Treatments**

Breast cancer treatments do carry risks of morbidity and even mortality. Morbidities reported include cardiac complications, second cancers, wound infections, peripheral neuropathy, lymphedema, impaired range of shoulder motion, and psychological distress. Of these, the morbidity of greatest incidence is lymphedema (swelling of lymph vessels as a result of fluid buildup). Immediate morbidity from RT is typically reported in the form of dermal reactions, but long-term consequences can include increased cardiac mortality and new cancers.<sup>33</sup>

An estimated 30% of all breast cancer cases (both invasive and DCIS) are considered to be overdiagnosed and overtreated. Overdiagnosis is diagnosis of cancers that would not have presented within the life of the patient. Overtreatment can occur in two ways—either in overdiagnosis, where any treatment is unnecessary, or with the administration of more aggressive therapies than is necessary.<sup>34</sup> It has recently been estimated that one to three deaths from overtreatment occur for every one breast cancer death avoided.<sup>35</sup>

## **Drug Development**

In May 2012, the Pharmaceutical Research and Manufacturers of America reported that there were currently 991 medicines and vaccines in clinical testing for the treatment of cancer, including 111 specific for breast cancer.<sup>36</sup> In addition, there are many clinical trials evaluating existing drugs in new combinations or at different stages of disease. A recent search of [ClinicalTrials.gov](http://ClinicalTrials.gov) shows 1,600 clinical trials are currently ongoing or recruiting for the evaluation of drug interventions for breast cancer.<sup>37</sup> There are clearly many interventions and trials in breast cancer. What remains unknown is whether the current approaches of developing more drugs and conducting more clinical trials can be redesigned to accelerate the rate of progress that will end breast cancer.

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- <sup>1</sup> Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, and Bray, F. 2013. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer. Available from <http://globocan.iarc.fr>, accessed on March 19, 2014.
- <sup>2</sup> American Cancer Society. Cancer Facts & Figures 2014. Atlanta. American Cancer Society, Inc.
- <sup>3</sup> Altekruse S, Kosary C, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975-2007, Bethesda, Maryland, National Cancer Institute.
- <sup>4</sup> Anderson W, Katki H, and Rosenberg P. 2011. Incidence of breast cancer in the United States: Current and future trends. *J Natl Cancer Inst* 103(18):1397-1402.
- <sup>5</sup> Allegra CJ, Aberle DR, Ganschow P, et al. 2009. NIH state-of-the-science conference statement: Diagnosis and management of ductal carcinoma in situ (DCIS). *NIH Consens State Sci Statements* 26(2):1-27.
- <sup>6</sup> Howlader N, Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2008, National Cancer Institute, Bethesda, Maryland, [http://seer.cancer.gov/csr/1975\\_2008/](http://seer.cancer.gov/csr/1975_2008/), based on November 2010 SEER data submission, posted to the SEER website, 2011.
- <sup>7</sup> Chlebowski, RT, Manson JE, Anderson GL, et al. 2013. Estrogen plus progestin and breast cancer incidence and mortality in the women's health initiative study. *JNCI J Natl Can Inst*. <http://jnci.oxfordjournals.org/content/early/2013/03/21/jnci.djt043.abstract>, accessed on April 16, 2013.
- <sup>8</sup> Welch HG, Schwartz LM, and Woloshin S. 2000. Are increasing 5-year survival rates evidence of success against cancer? *JAMA* 283(22):2975-2978.
- <sup>9</sup> Harris JR, Lippman ME, Morrow M, et al (eds). 2000. *Diseases of the Breast*, 2nd ed. Philadelphia: J.B. Lippincott, Williams & Wilkins.
- <sup>10</sup> Grandishar W, Northwestern University, Metastatic Breast Cancer Network <http://mbcn.org/education/category/statistics/>.
- <sup>11</sup> Pal SK, et al. 2008. Lack of survival benefit in metastatic breast cancer with newer chemotherapy agents: The City of Hope cancer experience. ASCO Breast 2008, Abstract 95.
- <sup>12</sup> PHARMA: Decision Resources 2012 Oncology Patient Flow Model: Breast Cancer.
- <sup>13</sup> Jatoi I, Chen BE, Anderson WF, et al. 2007. Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. *J Clin Oncol* 13:1683-1690.
- <sup>14</sup> Yu KD, Wu J, Shen ZZ, et al. 2012. Hazard of breast cancer-specific mortality among women with estrogen receptor-positive breast cancer after five years from diagnosis: Implication for extended endocrine therapy. *J Clin Endocrinol Metab* 97(12):E2201-E2209.
- <sup>15</sup> Ziegler RG, Benichou J, Byrne C, et al. 1995. Proportion of breast cancer cases in the United States explained by well-established risk factors. *J Natl Cancer Inst* 87(22):1681-1685.
- <sup>16</sup> American Cancer Society. 2010. *Breast Cancer Facts & Figures 2009-2010*. <http://www.cancer.org/acs/groups/content/@nho/documents/document/f861009final90809pdf.pdf>, accessed on April 16, 2013.

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- <sup>17</sup> National Cancer Institute FactSheet: Breast Cancer Risk in American Woman. <http://www.cancer.gov/cancertopics/factsheet/detection/probability-breast-cancer>, accessed on April 16, 2013.
- <sup>18</sup> Chlebowski RT, Chen Z, Cauley JA, et al. 2010. Oral bisphosphonate use and breast cancer incidence in postmenopausal women. *J Clin Oncol* 28(22):3582-3590.
- <sup>19</sup> Rennert G, Pinchev M, and Rennert HS. 2010. Use of bisphosphonates and risk of postmenopausal breast cancer. *J Clin Oncol* 28(22):3577-3581.
- <sup>20</sup> Gnani M. 2010. Can oral bisphosphonates really reduce the risk of breast cancer in healthy women? *J Clin Oncol* 28(22):3548-3551.
- <sup>21</sup> Chlebowski RT, McTiernan A, Wactawski-Wende J, et al. 2012. Diabetes, metformin, and breast cancer in postmenopausal women. *J Clin Oncol* 30(23):2844-2852.
- <sup>22</sup> Ma H, Hill CK, Bernstein L, et al. 2008. Low-dose medical radiation exposure and breast cancer risk in women under age 50 years overall and by estrogen and progesterone receptor status: Results from a case control and case-case comparison. *Breast Cancer Res Treat* 109(1):77-90.
- <sup>23</sup> Pijpe A, Andrieu N, Easton DF, et al. 2012. Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: Retrospective cohort study (GENE-RAD-RISK). *BMJ* 2012 Sep 6; 345:e5660.
- <sup>24</sup> Formenti SC, Preston-Martin S, and Haffty BG. 2000. BRCA1/2 germline mutations: A marker for radioresistance or radiosensitivity? *J Clin Oncol* 18(5):1159-1160.
- <sup>25</sup> Giuliano AE, Hunt KK, Ballman KV, et al. 2011. Axillary dissection vs. no axillary dissection in women with invasive breast cancer and sentinel node metastasis. *JAMA* 305(6):569-575.
- <sup>26</sup> National Comprehensive Cancer Network: Breast Cancer NCCN Guidelines for Patients. <http://www.nccn.org/patients/guidelines/breast/index.html>, accessed on April 16, 2013.
- <sup>27</sup> Early Breast Cancer Trialists' Collaborative Group. 1988. Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28,896 women. *N Engl J Med* 319(26):1681-1692.
- <sup>28</sup> Early Breast Cancer Trialists' Collaborative Group. 1992. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 339(8784):1-15.
- <sup>29</sup> Multi-agent chemotherapy for early breast cancer. Cochrane Database Syst Rev 2002(1):CD000487.
- <sup>30</sup> Fisher B, Anderson S, Bryant J, et al. 2002. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 347(16):1233-1241.
- <sup>31</sup> Clarke M, Collins R, Darby S, et al. 2005. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 366(9503):2087-2106.

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- <sup>32</sup> Mariotto AB, Yabroff KR, Shao Y, et al. 2011. Projections of the cost of cancer care in the United States: 2010-2020. *J Natl Cancer Inst* 103(2):117-128.
- <sup>33</sup> Darby SC, McGale P, Taylor CW, et al. 2005. Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: Prospective cohort study of about 300,000 women in US SEER cancer registries. *Lancet Oncol* 6(8):557-565.
- <sup>34</sup> Bleyer A and Welch HG. 2012. Effect of three decades of screening mammography on breast cancer incidence. *N Engl J Med* 367(21):1998-2005.
- <sup>35</sup> Baum M. 2013. Harms from breast cancer screening outweigh benefits if death caused by treatment is included. *BMJ* 346:385-386.
- <sup>36</sup> PhRMA, The Pharmaceutical Research and Manufacturers of America. 2012. *Medicines in Development: Cancer*.  
<http://www.phrma.org/sites/default/files/pdf/phrmamedicinesindevelopmentcancer2012.pdf>, accessed on April 16, 2013.
- <sup>37</sup> [Clinicaltrials.gov](http://Clinicaltrials.gov), search terms breast cancer and interventions, accessed on March 24, 2014.